REMARKS/ARGUMENTS

In response to the Office Action of January 16, 2007, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

New claims 15-17 have been added. Claims 1-4 have been cancelled. Claims 13 and 14 were cancelled in a previous response (filed on June 27, 2005). Claims 5-12 are withdrawn from consideration. It is understood that claims 5-12, drawn to the non-elected invention, will remain pending, albeit withdrawn from consideration on the merits at this time. Applicants wish to preserve their right to present claims 5-12 in a divisional application(s).

Rejections under 35 USC 112, first paragraph

The rejection of claims 1-4 under 35 USC § 112, first paragraph, as set forth at ¶ 6 of the previous office action (01/04/2006) has been maintained for reasons of record insofar as it is applied to new claims 15-17, which replace canceled claims 1-4.

Claims 15-17 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detection of thrombospondin, is alleged by the Examiner to not reasonably provide enablement for diagnosis of Alzheimer's dementia via detection of a thrombospondin polypeptide in a body fluid sample from a mammal. The specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Newly added claims 15-17 are broadly drawn to a method for diagnosing Alzheimer's dementia in a mammal, determining a presence of a thrombospondin polypeptide in a body fluid sample from said mammal by contacting the sample with at least one antibody which specifically binds to a thrombospondin polypeptide weighing about 180 kDa, wherein the presence of said thrombospondin polypeptide is diagnostic for Alzheimer's dementia.

The Examiner acknowledges that at page 10 of the response filed July 10, 2006, Applicants have argued that Figures 1 and 2 of the instant specification provide data evidencing that a thrombospondin polypeptide weighing about 180 kDa was identified in samples obtained from patients with Alzheimer's disease but not in samples obtained from age-matched controls. Applicants

have asserted that the 180 kDa thrombospondin polypeptide is shown to be a marker of Alzheimer's dementia and further assert that the instant specification fully enables a method of diagnosing Alzheimer's dementia by determining the presence of a thrombospondin polypeptide weighing about 180 kDa in a sample.

The Examiner has considered Applicants' arguments, but they have not been deemed to be persuasive. The description of Figure 2 (p. 21 in the instant specification states that the 180 kDa band for thrombospondin is "not visible in 11 of the 15 age-matched controls.

From Fig. 2 it can be seen that all 13 AD samples show positive, 11 of the normals show negative, 4 of the age-matched controls show negative with possible dementia." However, the Examiner has indicated that this does not match what is shown in Figure 2. The Examiner notes that there are nine (9) "normal" controls samples (designated with an "N") and eighteen (18) Alzheimer's disease (designated with "AD") samples shown in Figure 2, wherein three of the AD samples (ADH39, ADO003, and ADO005) are negative for the 180 kDa band. Thus, the Examiner asserts that there are at least four cases in which individuals with possible dementia tested negative and three cases in which patients already diagnosed with Alzheimer's disease also tested negative for the thrombospondin polypeptide weighing about 180

kDa. Therefore, contrary to Applicants' assertions, based on the description for Figure 2 and Figure 2 itself, the Examiner has concluded that it is clear that thrombospondin is not a specific marker for diagnosing Alzheimer's dementia because there is not an accurate correlation between the disease and presence of the polypeptide.

In summary, the Examiner concludes that it would not be expected that one of ordinary skill in the art could successfully make and use the instant invention as broadly claimed without undue experimentation, and that the claims merely represent an invitation to experiment to discover how to use Applicants' invention.

Applicants believe that the problem here is that the findings of which Applicants speak regarding the Figures have been lost in the reproduction of these figures during the image capture process.

Applicants' representative will confer with the Examiner and attempt to place in her possession a better copy of the figure which will demonstrate that which the Applicants state is depicted therein.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention.

Newly presented claim 15 recites the phrase "a thrombospondin polypeptide weighing about 180 kDa", which is indefinite because the claim does not specify the manner in which the molecular weight was determined (native PAGE, denaturing SDS¬PAGE, predicted from sequence, etc.) It is well known in molecular biology that the value of the molecular weight for a given protein depends entirely upon the manner in which it is determined. Therefore, the recitation of the molecular weight in the claim is not meaningful, as the metes and bounds of the claim cannot be ascertained.

Claims 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for being dependent from indefinite rejected claim 15.

It is respectfully submitted that the specification, at p. 19, l. 18 first states that the samples were treated as follows:

"Spin, analyze the supernatant by 1D gel electrophoresis. Heparin-conjugated agarose beads were used as an affinity column to pull down all heparin-binding molecules in AD and age-matched control sera samples.

The specification goes on to state, at page 19, l.24 - p. 20, l.1 that:

"The affinity column purified samples were run on a 10-20% precast tricine gel, supplier Invitrogen."

Lastly, at p. 20, lines 10-18, it is stated that:

"This band in gel digested with trypsyn was sequenced by QSTAR Pulsar I (MDS Sciex) mass spectrometry. Five most intensive peaks of trypsyn peptide were sequenced and all of these match to thrombospondin. The arrow indicates the 180 kDa band that show up in all the AD samples and are not visible in 11 of the 15 age-matched controls. From Fig.2 it can be seen that all 13 AD samples show positive, 11 of the normals show negative, 4 of the age-matched controls show negative with possible dementia."

Thus it is clear that gel electrophoresis was the methodology utilized to determine the 180 KDA weight of the Thrombospondin peptide.

Rejection Under 35 USC 102(e):

The rejection of claims 1-4 under 35 USC § 102(e), as set forth at paragraph 11 of the previous office action (01/04/2006) has been maintained for reasons of record insofar as it is applied to new claims 15-17, which replace canceled claims 1-4. Newly added claims 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,605,592, to Ni et al. or in the alternative US PGPub 20020068319 by Ni et at., as evidenced by Asakura et al. (J. Neuroimmunol. 1996; 65:11-19). The Ni et al. references are cumulative and are therefore cited together with identical reasoning therefore.

At page 18 of the response filed July 10, 2006, Applicants have previously asserted that Ni et al. does not teach a thrombospondin peptide, but a peptide that shares some similar

domains with thrombospondin. Applicants further argue that even if Ni et al. did disclose thrombospondin, they do not teach a polypeptide subunit of thrombospondin-1 weighing about 180 kDa that was identified as present in Alzheimer's patients and absent in control patients and thus useful as a marker for diagnosing Alzheimer's disease. Applicants have thus asserted that Ni et al. cannot be said to either expressly or inherently describe each and every element in the claims as now presented for examination.

Applicants' arguments have been fully considered by the Examiner, however they are not deemed to be persuasive. Ni et al. teach a novel THRAP protein that exhibits 13 thrombospondin-1 (TSP-1)-like domains, IgG-like domains and proteinase inhibitor-like domains, as in Figure 4. It is also noted that Figure 5 of the patent shows the regions of identity between the amino acid sequence of THRAP and the translation product of thrombospondin-like protein as determined by BLAST analysis. Further, Ni et at. disclose that the predicted molecular weight of the THRAP protein is about 191 kDa (see column 24, lines 46-47), which is "about 180 kDa" as instantly recited. Thus, the Examiner alleges that the THRAP protein disclosed by Ni et al. bears striking homology to TSP-1, both in terms of its amino acid sequence and its predicted weight, and would thus meet the limitation of "a thrombospondin polypeptide weighing about 180

kDa." The takes the position that the recitation of the molecular weight in the claims is not meaningful, and Ni fully anticipates this limitation. Moreover, the Examiner asserts that Ni et al. teach an analysis of the THRAP amino acid sequence (Figure 6), with highly antigenic regions of the THRAP protein identified, i.e., regions from which epitope-bearing peptides of the invention can be obtained.

New claims 15-17 recite a method for diagnosing Alzheimer's dementia comprising contacting a sample of a body fluid with at least one antibody which specifically binds to a thrombospondin polypeptide weighing about 180 kDa and determining the presence of said thrombospondin polypeptide in said sample.

The Examiner then posits that the diagnostic method thus hinges on the specificity of the antibody for binding to a thrombospondin polypeptide in order to detect the polypeptide's presence, and that because of the tremendous overlap in amino acid sequence and antigenic epitopes between the THRAP protein disclosed by Ni and the thrombospondin protein, it would be expected that the antibodies disclosed by Ni for detection of THRAP protein and diagnosis of Alzheimer's disease would be capable of detecting thrombospondin and diagnosing Alzheimer's dementia as instantly claimed.

The Examiner grounds this theory on the basis that antibodies, even monoclonal antibodies, are notoriously promiscuous in terms of their capacity to bind similar epitopes on different proteins. Finally, as noted in the previous office action, the Examiner reiterates that Ni et al. teach that the protein may be detected in bodily fluids such as lymph, serum, plasma, urine, synovial fluid and spinal fluid, taken from an individual having the disorder and compared to a sample from an individual not having the disorder. Additionally, Ni et al. disclose various immunoassay techniques for detecting a polypeptide of the invention, including, but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassay, ELISA, "sandwich" immunoassays, western blots, precipitation reactions, etc. (see column 186, lines 45-67). Ni et al. teach that detection of THRAP polypeptide and/or fragments thereof in a biological sample is useful for the diagnosis of Alzheimer's disease (see column 91, lines 27-37). Accordingly, the Examiner concludes that the teachings of Ni et al. anticipate instant claims 15-17.

Applicants strongly disagree with the position taken by the Examiner. Contrary to the Examiner's assertions, THRAP is simply not equivalent to thrombospondin, the claimed molecular weight of about 180 (as established via gel electrophoresis) is, in fact,

different from the "about 190" of Ni et al, and it is well-established that any changes to the sequence of a peptide may very well have a substantial effect on binding, and therefore the ability of a diagnostic assay to function with the degree of sensitivity and specificity required.

If a rejection is maintained under 35 USC 102, it is given to mean that every limitation of the claim is set forth in the reference. This would not seem to be the case here. Alternatively, perhaps the Examiner is alleging "inherency" as a means of rationalizing maintaining the Ni et al disclosure as anticipatory of the claimed invention. It is respectfully submitted that such a presumption of inherency is not sufficient for maintenance of a rejection under 35 USC 102.

Given the known unpredictability of the art and the degree of experimentation required to ascertain such facts as the Examiner alleges, it is respectfully submitted that the propriety of such a rejection must fail based upon a review of the Wands factors. In all due respect to the Examiner, the allegation of anticipation over Ni is simply not justified and is certainly not supported by any factual underpinnings sufficient to constitute anticipation within the meaning of 35 USC 102. The identification of a unique protein "THRAP" in the '592 patent as an angiogenesis regulating protein which shares regions of

identity with the translation product of "thrombospondin-like protein" would seem to be a far cry from a teaching that THRAP is equivalent to the thrombospondin peptide of the instant invention. Certainly it can not be determined that the THRAP protein of the '592 having a predicted molecular weight of about 191, is anticipatory of the claimed "about 180 kda" peptide of the instant claims, and has the same physiological activity a relative to Alzheimer's disease, binding characteristics, etc. thereof.

For these reasons it is respectfully requested that the rejection over Ni et al be withdrawn.

CONCLUSION

In light of the foregoing remarks and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

Ferris H. Lander
Registration # 43,377

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)